submitted in response to the Office Action issued October 11, 2001.

The Invention is Enabled

Claims 1 and 4-15 have been rejected under 35 U.S.C. §112, first paragraph. The Examiner has admitted the instant Specification is enabling for a method for increasing the tolerance of a mammal to transgenic cells, wherein the transgenic cells are produced *in vivo* after the administration of a vector carrying a transgene that encodes for a protein. Such a method involves the administration of p15-deoxyspergualin (DSG) to the mammal intravenously or intraperitoneally before, during, or after administration of the vector, and a concomitant immunosuppressant therapy is discontinued. However, the Examiner has asserted that the instant Specification does not provide any guidance as to (1) how a transgenic cell would be prepared *in vitro*, (2) how a transgenic cell would be administered to a mammal, (3) what dosage of the transgenic cell would be administered, and (4) how the p15-deoxyspergualin would be administered. Thus, it is the Examiner's opinion that one of ordinary skill in the art would need to perform "extensive experimentation" to administer DSG, to determine the efficacy of DSG administered via different routes, and what dosages would be required to produce the increase in tolerance.

In response, Applicants initially submit that *in vitro* methods for producing a transgenic cell are known to those of ordinary skill in this art. For example, US Patent 6,063,593 entitled "TGFβ1 Responsive Bone Marrow Derived Cells To Express A Recombinant Protein" claims a method of *in vitro* transfection of mammalian cells and suggests using such transfected cells in gene therapy. Since such methods are known to those of ordinary skill in the art, they need not be described in detail in the instant Application. Indeed, guidelines published in Fed. Reg.,

66(4):1105 (Jan. 5, 2001) make clear that:

> Information which is well known in the art need not be described in detail in the specification....
>
> What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not specifically described in the specification, then the adequate description requirement is met.

Fed. Reg., 66(4):1105 (Jan. 5, 2001).

Furthermore, the Examiner is incorrect in asserting that extensive experimentation is required to deliver DSG by routes other than intravenously or intraperitoneally. On the contrary, Applicants submit that ***at most***, the use of merely routine laboratory techniques may be needed for other types of administration. As explained, above, the guidelines make clear that what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. Routine laboratory techniques for adapting a pharmaceutical to various types of delivery methods are well known, understood, and regularly practiced by those of ordinary skill in the art. It has been judicially held that if a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied. *In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); *In re Hitchings*, 342 F.2d 80, 87, 144 USPQ 637, 643 (CCPA 1965). See also *In re Brana*, 51 F.2d 1560, 1566, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993). Consequently, this rejection should be withdrawn.

Similarly, the determination of dosages of transgenic cells and DSG requires merely the use of routine laboratory techniques. Such techniques are well known, understood, and regularly

performed by skilled artisans. MPEP § 2164.01(c) makes clear that:

> ...it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph.

Moreover, the Examiner has provided no scientific basis for the assertions that "extensive" experimentation is required practice the instant Invention, or indeed, even what the term means. Hence, in light of the above, it is respectfully submitted that the pending Claims are enabled, and that these rejections are obviated.

Furthermore, the Examiner has questioned the integrity of data presented in the Specification. The Examiner has acknowledged that Example 1 teaches that in 50% of the mice treated with DSG for five (5) days after vector administration, 10% of the maximal expression of the transgene was observed on the 42nd day. However, the Examiner has also asserted that a PNAS paper cited on page 8 of the instant Specification teaches the construction of adenovirus vectors that have deletions or insertions in the E1 or E3 regions, and that different vectors taught in the PNAS paper would produce different levels of immune response. Thus, it is the Examiner's opinion that it is unclear whether DSG contributed to the maintenance of the level of β-galactosidase in the mice, or whether the deletion of different genes in the adenovirus contributed to the observed results.

Furthermore, the Examiner has questioned whether the transgene used in the experiments reported in the instant Specification contributed to the reported results. In particular, the

Examiner has noted that Example 2 in the Specification describes the effect of DSG on the expression of α1-antitrypsin by an adenoviral vector in an NMRI mouse, and that administration of DSG i.p. for five (5) days resulted in about a six (6) fold difference in the serum level of α 1-antitrypsin at almost all of the time intervals studied. However, it is the Examiner's belief that the instant Specification teaches that alpha 1-antitrypsin used in Example 2 is not antigenic. Thus, it is the Examiner's opinion that the higher protein levels in Example 2 could be due to lack of antigenicity of the transgene product, and that a skilled artisan would need to carry out experimentation of trial and error to determine whether DSG would have provided protection when different transgenes are used in the claimed method.

In response, Applicants respectfully submit the Examiner's assertions lack merit. Initially, the Examiner believes it is unclear whether DSG contributed to the maintenance of the level of β-galactosidase in the mice, or whether the deletion of different genes in the adenovirus contributed to the observed results. However, it is made clear at pages 9-10 of the instant Application that the ***identical vector*** was administered to both immunosuppressed mice and control mice. Consequently, the immunosuppressive effects of the vector itself or a gene product of the vector, ***if any***, would have no net effect on the results obtained and set forth in the instant Application.

Other assertions the Examiner made in rejecting the pending Claims are that (1) the state of the art of cell transplantation, except for autologous cell transplantation which would produce minimal immune response, is unpredictable, and that at the time of the invention gene therapy was unpredictable. In support of these assertions, the Examiner has cited Hardy and Marvin (Transplantation Proceedings 31:2949-2950, 1999) and Anderson WF (Nature 392 (SUPP):25-

30, 1998), respectively.

It is respectfully submitted, however, that these assertions are erroneous. Initially, with respect to cell transplantation, it is well known that allografts of tissues, organs, etc. which come from donors are transplanted into patients. Indeed, heart transplants, kidney transplants, liver transplants, bone marrow transplants are routinely performed. Moreover, gene therapy was clearly a predictable technique at the time of the filing of the priority document in this matter. The filing date for the priority document in this Application is March 21, 1997. Yet, since 1991, approximately 87 U.S. Patents have been issued that contain the phrase "gene therapy" in their title[1]. Indeed, a number of these issued patents were filed with the United States Patent and Trademark Office ***prior*** to March 21, 1997. Particular examples of such patents include patent number 5,399,346 to Anderson *et al.* entitled *Gene Therapy*[2], patent number 5,645,829 to Shockey *et al.* entitled *Mesothelial Cell Gene Therapy*[3], and patent number 5,821,235 to Henning *et al.* entitled *Gene Therapy Using the Intestine*[4]. In issuing these patents, the United States Patent Office has clearly admitted that at the time of filing the priority document in the instant Application, ***and even prior thereto***, gene therapy methods were readily available that were novel, useful, and most importantly, ***enabled***, i.e., did not require the performance of undue experimentation to perform the therapies. Thus, it is respectfully submitted the Examiner is simply not correct in asserting that gene therapy methods were not predictable at the filing date of the priority document in this matter.

Hence, for the foregoing reasons, it is respectfully submitted that the pending Claims in

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1 A copy of this list is attached hereto for the Examiner's review.
2 Filed March 30, 1994 and issued March 21, 1995.
3 Filed June 18, 1993 and issued July 8, 1997.

the Application are enabled, and that these rejections should be withdrawn.

The Invention is Novel

Claims 1, 4, 9, 10 and 12 have been rejected under 35 U.S.C. § 102(a) as being anticipated by the teachings of Smith *et al.* (Gene Therapy 3:496-502, 1996; abstract only). The Examiner has asserted that Smith *et al.* teach the use of a transient immunosuppression with DSG in mice injected intravenously with an adenoviral vector carrying the β-galactosidase gene. The Examiner also believes that Smith *et al.* teach the administration of DSG intravenously to mice at the time of exposure to the adenovirus, and the observation that the administration of DSG permitted an effective second administration of a factor IX vector, without any immunosuppression afterwards.

Furthermore, Claims 1, 4, 9, 10 and 12 have been rejected under 35 U.S.C. § 102(a) as being anticipated by the teachings of Trapnell *et al.* (WO 96/12406, 05-02-1996 (the '406 application)). The Examiner has asserted that the '406 application teaches a method for concurrently administering to mice an immunosuppressive agent, such as DSG, and an adenoviral vector that expresses a therapeutic gene of interest. It is the Examiner's position that page 42 of the '406 application teaches that after 5 weeks, no detectable levels of factor XI neutralizing antibodies were observed in the mice to which the vector and DSG were administered, and that re-administration of the vector was permissible.

Applicants respectfully traverse these rejections. Neither of the references teach each and every aspect of the instant Invention. Claim 1 of the instant Application is directed towards, *inter alia*, a method for increasing the tolerance of a mammal to transgenic cells. In Example 1 on

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4 Filed January 20, 1995 and issued October 13, 1998.

pages 8-9 of the instant Application, it is explained that a recombinant adenovirus which contained a β-galactosidase gene was administered to the mammal concomitantly with DSG. Applicants also explain that:

> The control group reaches a maximum of the reporter gene expression in the liver on the 6th day, the expression is then continuously reduced by the activity of the cytotoxic T cells and reaches the starting level after approximately 21 days....
>
> After discontinuing the immunosuppressants, the reporter gene expression in the cyclosporin A group fell to the starting level over a period of 21 days (42 days after vector administration) while in the DSG group a massive gene expression was still detectable.

(Page 9, lines 1-17 of the instant Application).

It is clear from the passages reproduced above that Applicants measured the amount of ***gene product encoded by a gene in the adenovirus, and not the amount of adenovirus itself.*** Furthermore, the instant Specification teaches that when practicing the instant Invention, the amount of gene product encoded by the adenovirus vector expressed in the cell increases relative to a that amount measured in control to which DSG is not administered. Hence consequently, the ***tolerance*** to the transgenic cells that produce the exogenous protein is increased. In stark contrast, neither Smith *et al.* nor the '406 application teach that tolerance to a ***transgenic cell*** is increased. For example, Smith *et al.* explain that:

> In the present study we demonstrate that the humoral immune response to a systematically administered adenovirus vector is dose dependent and can be modulated by a brief treatment with the immunosuppressive agents cyclophosphamide or deoxypergualin at the time of the initially treatment. This strategy permits effective multiple repeat doses of a vector encoding a therapeutic gene such as factor VIII or factor IX.

(Smith *et al.* p. 495).

Furthermore, on page 500, Smith *et al.* clearly state that "[w]e found that immuosuppression with DSG efficiently inhibited the humoral response to the ***vector*** and permitted an effective second administration (emphasis added). Thus, Smith *et al.* look for an antibody against the ***adenovirus vector***, and not against the gene product encoded by DNA contained in the adenovirus vector. Thus, Smith *et al.* provide no teaching that deoxypergualin can increase the tolerance to a transgenic cell transfected with an adenovirus. Consequently, Applicants' Invention is clearly novel with respect to the teachings of Smith *et al.*

Similarly, the '406 application also is concerned with modulating the immune response to the vector and not a gene product of the vector. In particular, on page 16 of the '406 application, it is explained that

> Applicants have found that, when compounds which prevent, suppress, or eliminate humoral immune responses to foreign antigens (such as, for example, deoxyspergualin, cyclophospamide, brequinar, leflunomide, mycophenolate, mofetil, anti-CD40 antibody, or anti-CD40 ligand antibody) are administered at a short time prior to, and/or during, and/or for a short time after adenoviral vector to a host, such compounds prevent the production of ***anti-adenoviral neutralizing antibodies*** in the host (emphasis added).

As explained above, a decrease in the production of antibodies to the vector teaches ***nothing*** with respect to increasing tolerance to the gene product and transgenic cells that produce the gene product. Hence, neither the teachings of Smith *et al.* nor the teachings of the '406 application anticipate the pending Claims in the instant Application, and these rejections should be withdrawn.

Fees

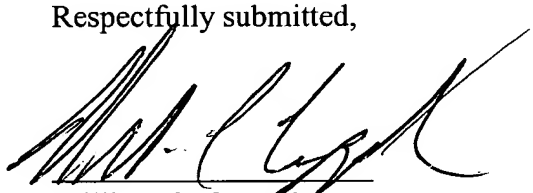
No fees are believed to be necessitated by the instant response. However, should this be

in error, authorization is hereby given to charge Deposit Account no. 18-1982 for any underpayment, or to credit any overpayments.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,



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March 29, 2002